

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/31, C07K 14/315, A61K 39/09,</b> <b>C12N 1/21, 5/10</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 98/24910</b> <b>(43) International Publication Date:</b> 11 June 1998 (11.06.98)
<b>(21) International Application Number:</b> PCT/US97/22125 <b>(22) International Filing Date:</b> 5 December 1997 (05.12.97) <b>(30) Priority Data:</b> 60/033,251 6 December 1996 (06.12.96) US <b>(71) Applicant (for all designated States except US):</b> REGENTS OF THE UNIVERSITY OF MINNESOTA [US/US]; Morrill Hall, 100 Church Street, S.E., Minneapolis, MN 55455 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SCHLIEVERT, Patrick, M. [US/US]; 5305 Birchcrest Drive, Edina, MN 55436 (US). OHLENDORF, Douglas [US/US]; 9397 Olympia Drive, Eden Prairie, MN 55347 (US). MITCHELL, David, T. [US/US]; 4217 Centerville Road, Vadnais Heights, MN 55127 (US). GAHR, Pamala, J. [US/US]; 2728 Horseshoe Lane, Woodbury, MN 55125 (US). <b>(74) Agent:</b> BRUESS, Steven, C.; Merchant, Gould, Smith, Edell, Welter & Schmidt, P.A., 3100 Norwest Center, 90 South Seventh Street, Minneapolis, MN 55402-4131 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims</i> <i>and to be republished in the event of the receipt of amendments.</i> <b>(88) Date of publication of the international search report:</b> 3 September 1998 (03.09.98)
<b>(54) Title:</b> MUTANTS OF STREPTOCOCCAL TOXIN C AND METHODS OF USE <b>(57) Abstract</b> <p>This invention is directed to mutant SPE-C toxins or fragments thereof, vaccine and pharmaceutical compositions, and methods of using the vaccine and pharmaceutical compositions. The preferred SPE-C toxin has at least one amino acid change and is substantially non-lethal compared with the wild type SPE-C toxin. The mutant SPE-C toxins can form vaccine compositions useful to protect animals against the biological activities of wild type SPE-C toxin.</p>		

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# INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 97/22125

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/31 C07K14/315 A61K39/09 C12N1/21 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GOSHORN SC ET AL: "Nucleotide sequence of streptococcal pyrogenic exotoxin type C." INFECT IMMUN, SEP 1988, 56 (9) P2518-20, UNITED STATES, XP002066997	1,11-14
A	see the whole document	2-10
Y	KLINE, J. BRADFORD ET AL: "Analysis of the superantigenic activity of mutant and allelic forms of streptococcal pyrogenic exotoxin A" INFECT. IMMUN. (1996), 64(3), 861-9 CODEN: INFIBR; ISSN: 0019-9567, XP002066999 see the whole document	1,11-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 June 1998

Date of mailing of the international search report

07.07.98

Name and mailing address of the ISA

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Authorized officer

Gurdjian, D

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22125

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NORRBYTEGLUND A ET AL: "DETECTION AND NUCLEOTIDE-SEQUENCE ANALYSIS OF THE SPEC GENE IN SWEDISH CLINICAL GROUP A STREPTOCOCCAL ISOLATES" JOURNAL OF CLINICAL MICROBIOLOGY, 1994, 32, 705-709, XP002066998 see the whole document ---	1-11
A	HOVDE CJ ET AL: "INVESTIGATION OF THE ROLE OF THE DISULFIDE BOND IN THE ACTIVITY AND STRUCTURE OF STAPHYLOCOCCAL-ENTEROTOXIN C1" MOLECULAR MICROBIOLOGY, 1994, 13, 897-909, XP002067000 see the whole document -----	1-11

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
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in its capacity as elected Office

Date of mailing (day/month/year) 23 July 1998 (23.07.98)	
International application No. PCT/US97/22125	Applicant's or agent's file reference 600.347WO11
International filing date (day/month/year) 05 December 1997 (05.12.97)	Priority date (day/month/year) 06 December 1996 (06.12.96)
Applicant SCHLIEVERT, Patrick, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

02 July 1998 (02.07.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Cruz Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 600.347WO11	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US97/22125	International filing date (day/month/year) 05/12/1997	Priority date (day/month/year) 06/12/1996
International Patent Classification (IPC) or national classification and IPC C12N15/31		
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 10 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 02/07/1998	Date of completion of this report 23.03.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer BULCAO DE MELO ... T Telephone No. (+49-89) 2399 8972 

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US97/22125

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-40 as originally filed

**Claims, No.:**

1-16 as originally filed

**Drawings, sheets:**

1/10-10/10 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**see separate sheet**

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 15 and 16.

because:

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- ☒ the said international application, or the said claims Nos. 15 and 16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US97/22125

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US97/22125

**SECTION I**

1. Amendments under Article 34 PCT:

Amended **pages 36-40 of the description**, filed with the demand (02.07.98) are considered to be unallowable under **Article 34 (2) (b) PCT** because they introduce subject-matter which extends beyond the content of the application as originally filed.

The substitution of the amino acid alanine by the amino acid serine in example 6 is not supported by the description because there is no specific reference therein to the preferential use of serine (instead of alanine, or any other of the mentioned amino acids) as the substitute amino acid in the amino acid change/s of the mutant SPE-C toxin.

Such subject-matter is regarded to be an information which is not directly and unambiguously derivable from that previously presented by the application.

Therefore, this International Preliminary Examination Report is established as if such amendments had not been made (**Rule 70.2 (c) PCT**).

**SECTION III**

2. According to **Article 34(4)(a)(I) PCT** and **Rule 67.1(iv) PCT** the International Preliminary Examination Authority is not required to carry out an international preliminary examination on an international application if, and to the extent to which, its subject-matter concerns methods for the treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

The subject-matter of **claims 15 and 16** relates to methods for treatment of the human or animal body. Therefore, no opinion with regard to novelty, inventive step and industrial applicability is established for said claims.

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EXAMINATION REPORT - SEPARATE SHEET**

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**SECTION V**

3. Reference is made to the following documents:

**D1:** Infect. Immun., Vol. 56, No. 9, 1988, pages 2518-2520

**D2:** Infect. Immun., Vol. 64, No. 3, 1996, pages 861-869

4. Novelty (**Article 33(2) PCT**)

The subject-matter of the present application does not appear to be disclosed in the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).

Therefore, in view of such prior art the subject-matter of the present application (**claims 1-14**) has to be regarded as being new (**Article 33 (2) PCT**).

5. Inventive Step (**Article 33 (3) PCT**)

The present application does not satisfy the criterion set forth in **Article 33 (3) PCT** because the subject-matter of **claims 1-14** does not involve an inventive step (**Rule 65 (1) and (2) PCT**).

The **closest prior art** to evaluate the inventiveness of **claims 1-14** is document **D1**, which discloses the nucleotide sequence of the gene *speC* encoding the streptococcal pyrogenic exotoxin type C (SPE-C). D1 also discloses that, among several members of a family of biologically and biochemically related toxins (type-A exotoxin from *Streptococcus pyogenes* (SPE-A), enterotoxins from *Staphylococcus aureus* and toxic shock syndrome toxin-1), of which SPE-C is a member, the mature amino acid sequence of SPE-C shared the greatest amount of homology with SPE-A.

Furthermore, D1 discloses that regions which are conserved between SPE-C and other toxins may represent biologically important sites or sites necessary for the structural integrity of the proteins, and further suggests studies using site-directed mutagenesis to analyse such regions.

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(See Abstract, Table 1, Figure 2 and page 2519, left hand column, lines 10-11 and right hand column, lines 20-26).

Starting from **D1**, the underlying **technical problem** to be solved by the present application can be considered to lie in the provision of mutant SPE-C toxins having at least one amino acid change and being nonlethal compared to the wild-type SPE-C.

In this respect, claim 1 merely states the problem to be solved, which problem is obvious in view of D1, without indicating in terms of technical features how this problem is to be solved. Given that a solution to a problem cannot be the problem itself, **claim 1** lacks inventiveness.

The **solution** provided by the Applicant to solve the above problem is represented by mutant SPE-C toxins having at least one amino acid change in one of the specific domains defined in claims 2 or at one of the specific amino acids indicated in claim 3.

Document **D2** discloses that extensive mutational analysis of SEB (*S. aureus* enterotoxin B) has defined amino acid residues important for interaction with either class II MHC molecules or the TCR, and therefore important for the superantigenic activity of SEB. D2 further discloses that SPE-A is closely related to SEB, and that amino acid identity with the above mentioned SEB residues allowed to determine the residues of SPE-A that interact with MHC-II and TCR. The SPE-A residues so determined were mutated, using site-directed mutagenesis, thereby identifying the residues of this toxin necessary for superantigenic activity and thus originating mutant SPE-A toxins having amino acid change/s, being nonlethal, having a decrease in mitogenicity...  
(See Abstract, page 863, left hand column, line 29-line 43 and Discussion).

Trying to solve the above technical problem, and taking together the teachings of **D1** and **D2**, the person skilled in the art would be taught to apply the strategy disclosed in D2 for the toxin SPE-A to the toxin SPE-C. Therefore, the person skilled in the art would not require any inventive skills to determine the SPE-C amino acid residues and domains responsible for different biological activities, such as toxicity and mitogenicity,

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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and then to use site-directed mutagenesis to originate SPE-C toxins mutated in said residues/domains.

Thus, the subject-matter of **claims 2-10** does not involve an inventive step.

Regarding the properties of the mutant SPE-C toxins, the provision of vaccine and pharmaceutical compositions comprising said mutant toxins is considered to be an obvious procedure to the person skilled in the art. Thus, the subject-matter of **claims 11 and 12** does not involve an inventive step.

The features of **claims 13 and 14** are generally known in the art. They do not confer as such an inventive step to the claimed subject-matter.

Said claims should relate to novel and inventive mutant SPE-C toxins.

6. Industrial Applicability (Article 33(4) PCT)

The subject-matter of **claims 1-14** is susceptible of industrial applicability as defined in **Article 33 (4) PCT**.

**SECTION VIII**

7. The present application does not satisfy the criterion set forth in **Article 6 PCT** because the following claims are not clear.

7.1. A toxin (**claim 1**) and a DNA (**claim 13**), regarded as chemical products, should be clearly and unambiguously characterized by technical features, e.g. their amino acid and nucleotide sequences, respectively, and not only by the result to be achieved (**cf. Guidelines for Preliminary Examination (PCT) CIII 4.7 and 4.7a**).  
Therefore, the subject-matter of **claims 1 and 13** lacks clarity.

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7.2. The term "fragment" renders **claim 1** unclear.

This term is vague and indefinite because it does not indicate either the length of the fragment, the region/domain of the toxin to which the fragment corresponds, the function of fragment, or any particular characteristic that the fragment should have.

Although in the description (page 22 line 22-page 23 line 8) said fragments are characterised, the meaning of a claim should be clear from the wording of the claim alone (see the **Guidelines for Preliminary Examination (PCT) CIII 4.2.**).

7.3. **Claim 1** lacks clarity due to the expression "at least one" regarding the amino acid changes in the mutant SPE-C toxin. The lack of an upper limit to define the maximum number of amino acid substitutions, as well as the lack of any other limiting feature (technical or functional), leads to a lack of clarity because without indicating how many (or which) amino acids are to be substituted, the subject-matter of claim 1 includes also mutant SPE-C toxins having all its amino acids changed, which no longer is a mutant SPE-C toxin but a completely different protein.

7.4. The expressions "substantially nonlethal" (**claim 1**), "substantially corresponding to wild-type SPE-C toxin" (**claim 1**), and "substantially enhance endotoxin shock" (**claim 10**) are not suitable to clearly define the scope of said claims, because they are without technical significance and their vagueness makes it entirely open to individual interpretation.

7.5. The term "SPE-C" (**claims 1-13**) is regarded as an acronym and should therefore be clarified.

7.6. **Claims 3-9** and example 6 refer to a mutant SPE-C toxin having an amino acid change at amino acid "asparagine-38". However, in the description (page 11, line 24) and in table 2, the substitution is at amino acid "asparagine-37". This inconsistency creates an ambiguity that should be removed by using always the same designation when referring to the same mutant toxin.

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International application No. PCT/US97/22125

- 7.7. It appears that the terms "SPE-A" (description: page 14, lines 12 and 22) and "speA" (description: page 26, line 31) are not correct, and that they should be replaced by the terms "SPE-C" and "speC", respectively.
- 7.8. The relation between the reference to fig. 2 (description: page 33, line 30) and figure 2 itself (drawings: sheet 2/10) is not clear. It appears that said reference to fig. 2 in the description is not accurate.

**SECTION VII**

8. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in documents **D1 and D2** is not mentioned in the description, nor are these documents identified therein.

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/22125

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 15 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>600.347WO11</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 97/ 22125</b>	International filing date (day/month/year) <b>05/12/1997</b>	(Earliest) Priority Date (day/month/year) <b>06/12/1996</b>
Applicant <b>REGENTS OF THE UNIVERSITY OF MINNESOTA et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☒ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
  - Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.
  - ☐ because the applicant failed to suggest a figure.
  - ☐ because this figure better characterizes the invention.
  - ☒ None of the figures.

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 97/22125

## B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 15 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

Remark on Protest: ☐ The additional search fees were accompanied by the applicant's protest and accompanied

☐ No protest accompanied the payment of additional search fees.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/22125

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/31 C07K14/315 A61K39/09 C12N1/21 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GOSHORN SC ET AL: "Nucleotide sequence of streptococcal pyrogenic exotoxin type C." INFECT IMMUN, SEP 1988, 56 (9) P2518-20, UNITED STATES, XP002066997	1,11-14
A	see the whole document ---	2-10
Y	KLINE, J. BRADFORD ET AL: "Analysis of the superantigenic activity of mutant and allelic forms of streptococcal pyrogenic exotoxin A" INFECT. IMMUN. (1996), 64(3), 861-9 CODEN: INFIBR; ISSN: 0019-9567, XP002066999 see the whole document --- -/--	1,11-14

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "&" document member of the same patent family

Date of the actual completion of the international search

8 June 1998

Date of mailing of the international search report

07.07.98

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22125

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NORRBYTEGLUND A ET AL: "DETECTION AND NUCLEOTIDE-SEQUENCE ANALYSIS OF THE SPEC GENE IN SWEDISH CLINICAL GROUP A STREPTOCOCCAL ISOLATES" JOURNAL OF CLINICAL MICROBIOLOGY, 1994, 32, 705-709, XP002066998 see the whole document ---	1-11
A	HOVDE CJ ET AL: "INVESTIGATION OF THE ROLE OF THE DISULFIDE BOND IN THE ACTIVITY AND STRUCTURE OF STAPHYLOCOCCAL-ENTEROTOXIN C1" MOLECULAR MICROBIOLOGY, 1994, 13, 897-909, XP002067000 see the whole document -----	1-11

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